Symptomatic Radionecrosis after AVM Stereotactic Radiosurgery.

Study of 16 Consecutive Patients

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Key words: stereotactic radiotherapy, radionecrosis, AVM

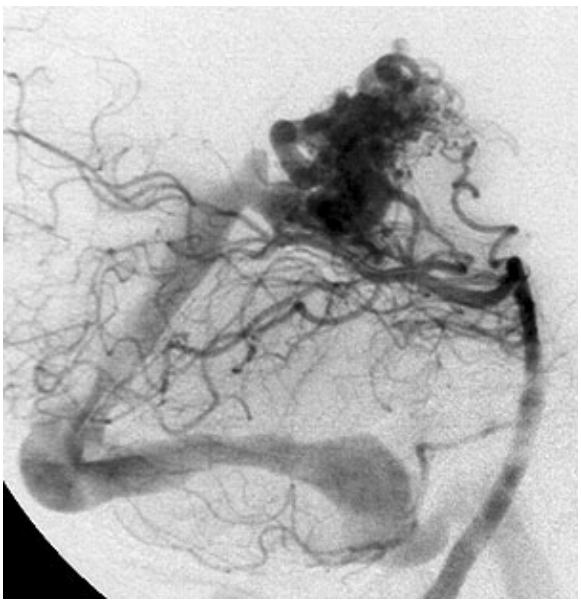
Summary

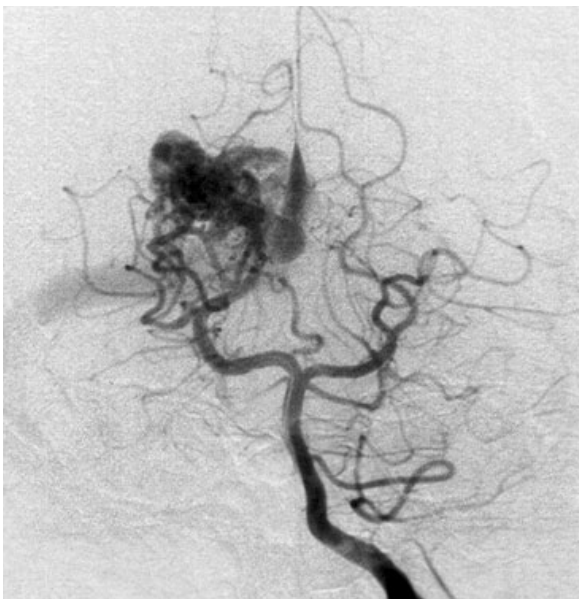
The purpose of our study was to analyze the outcome of symptomatic radionecrosis following stereotactic radiosurgery for brain arteriovenous malformations. Of 225 patients treated by linear accelerator radiosurgery for brain AVM, 16 (7,1%) presented post-radiosurgery symptomatic radionecrosis on a mean follow-up period of 50 months (range 1-123 months). Once diagnosed with radionecrosis, 14 of 16 patients were subjected to high dose corticotherapy consisting of escalating doses of dexamethasone for several weeks. The mean interval of occurrence of new symptoms was 11.6 months post-radiosurgery (range 6-20 months). The mean time of follow-up was 2.9 years post radiotherapy ranging from seven months to eight years. Of the 16 patients with symptomatic radionecrosis, 11 (68,75%) showed complete resolution of symptoms while five (31,25%) showed improvement but still presented a neurological deficit at the closing date of the study. At the closing date, 11 patients (68.75%) had angiographically completely obliterated arteriovenous malformations while another two patients had an obliteration of 95% to 98% and one patient had a 98% obliteration with development of a new contralateral AVM. In our series, symptomatic radionecrosis occurred in 7.1% of patients treated with stereotactic radiosurgery for brain AVM. These patients where subjected to a prompt, high dose corticosteroid treatment and most presented symptom resolution or improvement with a fair obliteration rate, offering protection from bleeding. Permanent neurologic deficits attributable to radionecrosis occurred in 2.2% of our patient population treated with stereotactic radiosurgery for brain AVM.

Introduction

Radiosurgery is a highly effective way of reducing the risk of haemorrhage in properly selected patients with cerebral arteriovenous malformations (AVM) [1-3]. Radiosurgery induces an injury response in the AVM nidus leading to eventual complete obliteration in 60 to 90% of cases, depending upon AVM size, configuration and the radiosurgery targeting and treatment techniques used [1-3]. AVM radiosurgery can sometimes unfortunately induce unwanted radiation injury in surrounding brain tissue [1,4-9]. Magnetic resonance (MR) scans shows postradiosurgery imaging changes in the brain surrounding an AVM in approximately 30% of patients, depending on the treatment volume and, to a lesser extent, the dose administered [7-10]. Fortunately, these effects are asymptomatic in two-thirds of affected patients, so that symptomatic radionecrosis develops only in approximately 9% of patients [7-10].

A





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The purpose of our study was to analyze the outcome of symptomatic radionecrosis in 16 consecutive patients treated for brain AVMs with focus on the severity and resolution of symptoms as well as the radioanatomic obliteration rate.

Methods

Patients

At the University Hospital of Nancy, 225 patients (114 men and 111 women) were treated with linear accelerator radiosurgery between July 1, 1992 and December 31, 2003. Of the 225 patients, two (0.8%) were lost to follow-up. The mean age was 36.2 years (range 13 – 69 years). All patients had only one AVM, but in 13 patients more than one target required irradiation. The patients were mainly referred after embolization in the neuroradiology department: The vast majority of patients presented with a complex AVM with a poor prognosis (failure of previous treatment, high Spetzler-Martin grade [11], large size, or initial haemorrhage) revealed by initial haemorrhage in 35.6% (80 of 225 patients). The main AVM diameter before embolization was < 30 mm in 60 (27%), between 30 and 59 mm in 122 (54.1%), and > 60 mm in 43 (18.9%) patients.

Treatment

Of the 225 patients, 165 (73,3%) had undergone previous treatment; 159 (70.6%) had previously undergone embolization alone, with a mean number of four sessions (range 1-13 sessions) and six (2.6%) had undergone both previous embolization and limited excision. Embolizations were performed under general anesthesia, with normal arterial blood pressure and systemic heparinization. In many cases, selective papaverine infusion was useful to prevent vasospasm. Cerebral AVM embolizations were performed by slowly injecting a mixture of cyanocrylate glue (Histoacryl, Braun Gmbh, Melsungen, Germany or Glubran, GEM, Viareggio, Italy) and iodized oil (Lipiodol, Ultrafluid, Guerbet, Aulnay, France) under biplane control. In most cases, a low concentration (cyanocrylate glue 20-25%) was preferred but a high concentration of pure glue was sometimes necessary when treating direct arteriovenous fistulas.

Radiosurgery

All patients had only one AVM. The radiosurgical technique was arc-therapy as described by Betti et Al [17]. All patients underwent CT and angiography to define the right coordinates of the AVM according to the Fisher stereotactic frame. Treatment was performed using a Saturn 43 linear accelerator (GE/Varian) delivering 10-MV photons. The patient lays supine on a dedicated couch, attached by the stereotactic frame to a stand.

Radiosurgery involved irradiation of one target in 222 (98.6%), two targets in 12 (5.3%),

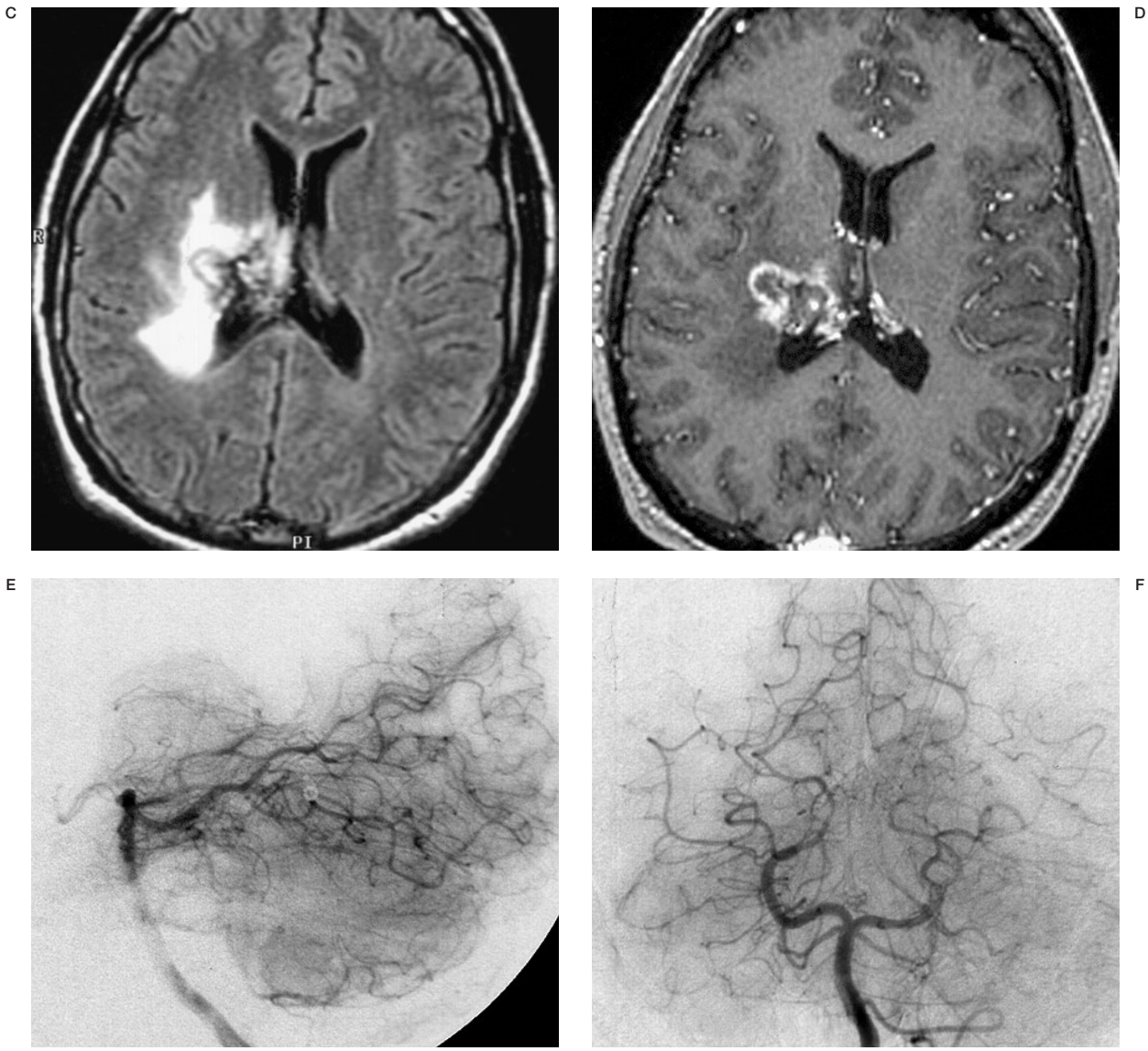
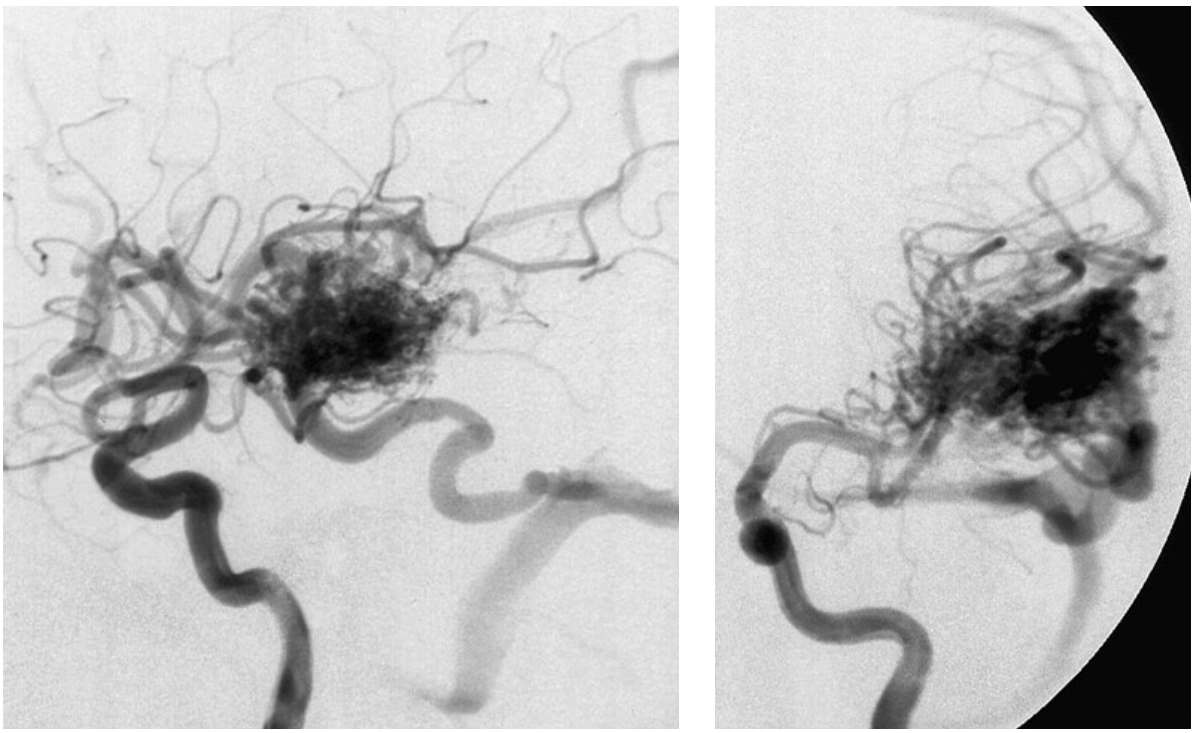


Figure 1 Case 2. A 29-year-old man, a very active farmer with a right thalamic AVM presenting with two episodes of haemorrhages that left a residual left hemiparesis (A,B). One embolization attempt was performed but was interrupted but because of the angioarchitecture of the lesion and the patient was referred for stereotactic radiosurgery. A multileaf collimator was used to irradiate a target of 14.6 cm^3 with a treatment dose of 18 grays. Six months post radiosurgery the patient's symptoms got worse. MRI showed edema on T2-weighted images (C) and rim enhancement on T1-weighted post-gadolinium enhanced images (D) characteristic of radionecrosis. A corticotherapy treatment was instituted for two months. 18 months latter the symptoms resolved to the point before radiosurgery. Control angiography two years post-radiosurgery showed complete radioanatomical cure of the arteriovenous malformation (E,F).

and three targets in one (0.4%) of the 225 patients. All the treatments were delivered with a single isocenter per target. A round collimator was used in 193 while a multileaf collimator was used in 32 patients. When a round collimator was used the mean collimator diameter was 22.6 mm (7 to 30 mm) with a mean number of 6.5 arcs (4 to 10) while when a multileaf collimator was used when mean number of arcs performed was nine (8 to 10). The mean sum of the target volumes per patient was 4.9 cm^3 (range 0.14 to 34.3 cm^3).

The prescription of the peripheral dose depended on the size and location of the AVM. Our dose prescription recommendations evolved with time. From September 30, 1992 to July



9, 1993, the dose was between 15 and 20 Gy for AVMs >20 mm in diameter and between 20 and 25 Gy for AVMs <20 mm. From July 9, 1993 onward, the dose was between 15 and 18 Gy for AVMs >20 mm in diameter and between 15 and 20 Gy for AVMs <20 mm. The AVM doses at the smaller end of the range were prescribed in the case of an AVM located in a functional or critical area. The mean peripheral dose, defined as the minimal dose to the AVM, was 17.2 Gy (range 10-25 Gy), and the mean maximal dose was 24.1 Gy (range, 17.1-35.7 Gy). The mean interval between AVM diagnosis and radiosurgery was 6.5 years (range 0.34 to 32 years).

Definition of symptomatic post-radiosurgery neurological sequelae, treatment and follow-up

Symptomatic post-radiotherapy radionecrosis was defined as the onset of a new neurologic deficit post radiotherapy that could be attributed to a change seen on MR. MR changes ranged from a classical radionecrotic lesion with central rim or irregular nodular enhancement and oedema to only an oedematous reaction. The gravity of symptomatic radionecrosis was graded according to the Glasgow Outcome five-point scale: 1, good recovery; 2, moderate disability but autonomous; 3, severe disability and loss of autonomy; 4, persistent vegetative state; and 5, death [12].

Once diagnosed with post-radiotherapy radionecrosis patients where subjected to high dose corticotherapy consisting of escalating doses of dexamethasone (range, 8 to 40 mg/d) for several weeks. Patients were followed clinically every six months by the same physician (L.P.) and underwent follow-up MRI at six months and angiography at two years and then annually until cure. Additional MRI was done in the case of suspicions of post-radiosurgery radionecrosis. The mean follow-up was 50 months (range, 1-123 months).

Statistical analysis

Statistical analysis was performed by using the chi-square and ANOVA tests with the SPSS 10.0 statistical package.

Results

Our study group consisted of 16 (7.1%) patients who fulfilled the criteria for post-radiotherapy radionecrosis (table). The mean interval of occurrence of new symptoms was 11.6 months (range 6-20 months). The main symp-

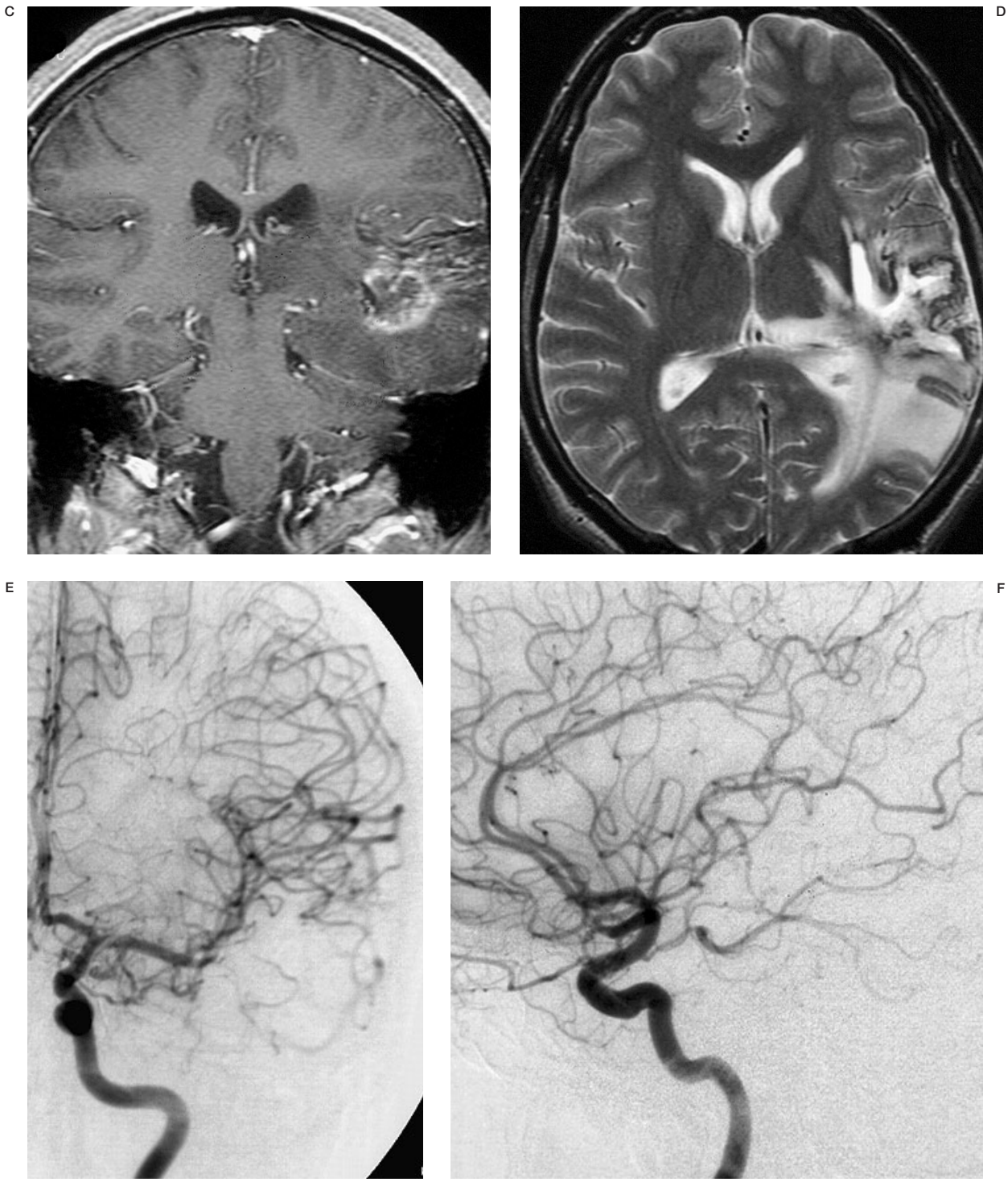


Figure 2 Case 10. A 24-year-old man with a left temporal arteriovenous malformation presenting symptoms of epilepsy, language problems and homonymous quadranopia (A,B). After three embolization sessions to reduce the malformation, stereotactic radiosurgery was performed on a volume of 14.6 cm^3 with a treatment dose of 16 gray. Six months post radiotherapy the patient reported mild amnesia, difficulties to understand spoken language and, while he was under antiepileptic treatment, an epileptic crisis. Post contrast T1 coronal (C) and axial T2-weighted (D) MRI images showed the characteristic ring enhancement and oedema of radionecrosis. Corticotherapy was instituted for five weeks. Seven months later these new symptoms had totally resolved. A control angiography performed two years after radiosurgery showed complete obliteration of the arteriovenous malformation (E,F).

Patient	Sex	Volume (cm^3)	Localization	Peripheral Dose (Gy)	Max Dose (Gy)	Previous Emboli-zations	Beam Number	Colli-mator	Time of onset post Rx (mo)	New Symptoms Type	Corctico therapy	Permanent sequelae	Post RX follow-up (months)	Obliteration
1	F	7,51	Deep R	18 & 18*	27,6	2	6 per target	25 per target	12	Hemiparesis	Y	Mild hemiparesis	78	95%
2	M	14,6	Deep R	18	22,5	1	9	ML	6	Hemiparesis aggravation	Y	None	24	obliterated
3	M	1,72	Temporal L	18	25,8	0	6	20	6	Epilepsy	Y	None	72	obliterated
4	M	6,4	Deep L	16	22	2	9	ML	12	Hemiparesis aggravation, visual disturbances	Y	None	24	obliterated
5	F	1,16	Deep L	25	35	2	6	15	10	Hemiparesis	Y	Mild hemiparesis	24	obliterated
6	F	1,58	Deep L	25	35	2	7	17,5	20	Hemiparesis	Y	Mild hemiparesis	96	98%
7	F	2,88	Deep L	20	28	5	6	20	8	Hemiparesis aggravation	Y	None	54	98% with new contralateral AVM
8	M	7,1	Parietal R	18	27	7	6	25	6	Diplopoia	N	None	7	lost for follow-up
9	F	7,48	Frontal post L	16	21,5	4	5	30	6	Epilepsy	Y	None	29	obliterated
10	M	14,6	Temporal L	16	20,4	3	9	ML	6	Epilepsy, mild aphasia and amnesia	Y	None	25	obliterated
11	F	12,5	Frontal post R	18	21,6	7	9	ML	18	Hemiparesis let upper limb	Y	None	24	obliterated
12	M	10,8	Parietal R	18	22	3	9	ML	18	Epilepsy	Y	None	27	obliterated
13	M	8,9	Cerebellar R	18	22	4	9	ML	7	Headache, Vertigo	N	None	7	awaiting
14	F	34,3	Parietal L	15	22	3	9	ML	12	Hemiparesis	Y	Hemiparesis	24	obliterated
15	M	7,95	Temporal L	17	24,5	7	6	30	12	Epilepsy	Y	None	24	obliterated
16	M	4,44	Temporal L	17,5	25	2	5	25	10	Epilepsy, hemiparesis, aphasia	Y	Moderate aphasia, professionally debilitating	26	obliterated

** Two targets. ML=multileaf collimator.*

tom was new onset or aggravation of epilepsy in four patients, hemiparesis in seven, diplopia in one patient, and a combination of symptoms including epilepsy, hemiparesis, aphasia, amnesia, visual disturbances, vertigo and headache in four patients.

The location of the treated arteriovenous malformations was: deep white matter or central nuclei in six patients, temporal lobe in four patients, parietal lobe in three, frontal posterior region in two and cerebellar lobe in one.

The mean irradiated volume in the patient group with symptomatic radionecrosis was 8.9 cm^3 (1.1 to 34.3 cm^3). Fifteen patients had one target irradiated while one patient had two. The dose administered to the periphery of the lesion was 18.3 Gy (15 to 25 Gy) while the maximum dose was 25.1 Gy (20.4 to 35 Gy). Fifteen patients had had embolizations of the arteriovenous malformation prior to radiotherapy with a mean of 3.6 embolization sessions (1 to 7 embolizations). Radiotherapy was administered with a round collimator in nine patients and with a multileaf collimator in seven patients. In the 225 patients treated with radiotherapy the likelihood of symptomatic radionecrosis was higher among patients treated using a multileaf collimator and was correlated with a tendency to treat larger arteriovenous malformations with the multileaf collimator ($p < .0001$).

Once the diagnosis of symptomatic radionecrosis was suspected clinically, patients where subjected to brain MRI. Thirteen patients (81.25%) showed a classic pattern of radionecrosis in the irradiation field corresponding to a mass with rim or nodular enhancement on T1-weighted images and a high signal surrounding oedema on T2-weighted images (figures 1 and 2). Three patients (18.75%) presented only oedematous changes on T2 weighted images.

Fourteen of the 16 patients diagnosed with symptomatic radionecrosis where subjected to high dose corticotherapy consisting of escalating doses of dexamethasone (range8 to 40 mg/Kg/d) for several weeks [13-16]. In two patients, high dose corticotherapy was not implemented because symptoms were judged as mild (headache and vertigo in patient 13 and diplopia in patient 8). The mean time of follow-up was 2.9 years post radiotherapy ranging from seven months to eight years.

Of these sixteen complications, five (2.2% of the total number of treated patients) were permanent (i.e., were still present at the closing date of the study). The other eleven complications were transient, with a median duration of 18 months (range 0-18 months). The seriousness of the complications was scored as 2 on the Glasgow outcome coma scale (autonomous with moderate incapacity) for all complications [12]. In all except one case of hemiparesis, post-radiosurgery symptoms improved or regressed completely. Permanent symptoms included one case of hemiparesis, three cases of moderate hemiparesis and one case of moderate, but professionally debilitating aphasia.

Follow-up MRI imaging was performed in ten patients, at a mean of 20.6 months (range 1 to 54 months) following the diagnosis of symptomatic radionecrosis. MRI showed residual oedema in five patients, residual enhancement in four patients and no residual lesion in one patient. At the date of the closure of this study 11 patients (68.75%) had completely obliterated arteriovenous malformations at control angiography while another two had an obliteration of 95% to 98% and one had a 98% obliteration with development of a new contralateral AVM. One patient was lost to follow-up, and one patient is awaiting two-year control angiography.

Discussion

Stereotactic radiotherapy is a well established method for treatment of arteriovenous malformations especially following previous nidus reduction with embolization. However, normal brain tissue surrounding the lesion may also be irradiated and late brain radiation injury or radionecrosis may ensue. This is particularly important in this young population of patients with a long life expectancy.

Symptomatic radionecrosis was observed in 16 of 225 patients treated with stereotactic radiosurgery for brain AVM (7.1%) with permanent symptoms in five patients (2.2%). The literature reports a rate of 0% to 22% [17-26] with permanent complications in 0% to 9.6% [8,18-20, 22,27-31]. Friedman et Al [20] reported a series of 158 patients treated by radiosurgery for AVM. They observed only two cases of symptomatic permanent radionecrosis (1%). Yamamoto et Al [25] reported a series of 40 patients followed for > five years after radiosurgery. They observed three radiation-induced complications (7.5%), two of which were related to the late occur-

rence of cysts. We observed cyst formation in one patient. Miyawaki et Al [22] reported a series of 73 patients treated by radiosugery for large AVMs (>50% had a principal diameter of >30 mm). They observed 16 late complications (22%) owing to radionecrosis occurring within a mean time of 11 months [22].

We observed an increase in symptomatic radionecrosis in the group of patients treated with a new, multileaf collimator system. This increase was correlated (p<.0001) to a higher volume of target lesion treated. Radionecrosis is known to be related to a low number of embolizations [21] and a high peripheral dose [32]. Common risk factors for complications after radiosurgery reported in the literature include size, AVM localization, irradiated volume encompassed by the 12-Gy isodose and a peripheral dose higher than 20 Gy [8,22,33].

Most of the cases of symptomatic radionecrosis occurred after the irradiation of arteriovenous malfomations located in eloquent regions of the brain: in the deep white matter or central nuclei in six patients, temporal region in four patients, parietal in three and frontal posterior region posterior in two. Location dramatically affects whether postradiosurgery radionecrosis is symptomatic or not [7-9]. Flickinger et Al [34] classified AVM locations in order of increasing risk: frontal, temporal, intraventricular, parietal, cerebellar, corpus callosum, occipital, medulla, thalamus, basal ganglia, and pons/midbrain.

On imaging, symptomatic postradiosurgery neurological sequelae ranged from a typical radionecrotic reaction with ring enhancement in eight patients to nidal enhancement and oedema in five patients and only oedema in three patients. Two mechanisms are thought to be implicated: haematoencephalic brain barrier breakdown and capillary proliferation [28, 29]. In the ten patients who had a follow-up MRI, nidal enhancement and oedema tended to regress but some residual changes remained even after 4.5 years after the first symptoms.

Once diagnosed with symptomatic radionecrosis 14 patients where subjected to high dose corticotherapy consisting of escalating doses of dexamethasone (range 8 to 40 mg/d) for several weeks. Improvement of symptoms was noted in 12 patients with complete regression in nine. Corticosteroids are thought to reduce vasogenic oedema and sometimes, although not consistently, ameliorate symptoms [14-16,35-38].

At the date of closure of this study 11 patients (68,75%) had completely obliterated arteriovenous malformations at control angiography while another two had a satisfactory subtotal obliteration of 95% and 98%. Another patient had a 98% obliteration with development of a new contralateral AVM. One patient was lost to follow-up, and one patient is awaiting two-year control angiography. This obliteration rate is comparable to post-radiosurgery AVM obliteration rates quoted in the literature ranging from 47% to 80% [17-26].

Our 16 patients with symptomatic radionecrosis showed a 68.75% total obliteration rate. Five patients presented permanent symptoms, three of which were mild. All patients had a Glasgow outcome coma scale of 2. These where mostly large, deeply located, non-operable AVMs, not amenable to further embolization, and obliteration provided protection from further haemorrhage. Of course, the risk of permanent radionecrosis-induced symptoms must be added to the overall risk of embolization as well as the risk of haemorrhage during the latency period that follows radiosurgery. However symptomatic radionecrosis, although a serious complication, should not be considered catastrophic, since affected patients, when subjected to a prompt, high dose corticosteroid treatment, usually show improvement or regression of symptoms over time with a satisfactory obliteration rate, protecting them from bleeding.

Conclusions

Symptomatic radionecrosis following AVM stereotactic radiosurgery is usually reversible. Furthermore, patients show a fair radioanatomical cure rate comparable to the cure rate of AVMs after non-complicated radiosurgery.

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